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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,072	BROUGH, DOUGLAS E.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 11/13/2007 has been entered. Claims 1-34 are cancelled. Claims 35-53 are newly added. Claims 35-53 are pending and are currently under examination. Claim 43 was amended.

This application 10/586,072 is a 371 of PCT/US04/04891 filed on 02/19/2004, which is a Continuation-in-part of US application 10/373,249 filed on 02/24/2003, abandoned on 01/18/2007.

Specification

1. In the Non-Final office action dated 08/16/2007, the Examiner noted that the specification filed on 07/14/2006 stated CROSS-REFERENCE TO RELATED APPLICATIONS as follows: This patent application claims the benefit of International Patent Application No. PCT/US2004/004891, filed February 19, 2004, which claims the benefit of pending U.S. Patent Application No. 10/373,249 filed February 24, 2003. However, this statement appears to be incorrect and contradicts to the Application Data sheet (ADS) filed on 07/14/2006. Based on the ADS, this application 10/586,072 is a 371 of PCT/US04/04891 filed on 02/19/2004, which is a CIP of the US application number 10/373,249, filed on 02/24/2003.

In response, Applicant filed amendments to the specification on 11/13/2007 replacing paragraph 0001 with the following: This patent application is the U.S. national phase of International Patent Application No. PCT/US2004/004891, filed February 19, 2004, which is a

continuation-in-part (CIP) of abandoned U.S. Patent Application No. 10/373,249 filed February 24, 2003. Therefore, previous objection to the specification in this aspect is ***withdrawn***.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 35-53 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed by Applicant on 11/13/2007 adding new claims 35-53.*

Claim 35 reads as following: A method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising a non-group C adenoviral vector comprising (a) a nucleic acid sequence encoding an atonal- associated factor operably linked to a promoter that specifically functions in supporting cells of the inner ear and (b) a chimeric coat protein ablated for binding to a native adenovirus receptor and comprising a non-native ligand, which non-native ligand enhances uptake of the adenoviral vector by cells of the inner ear, wherein the nucleic acid sequence is expressed to produce the atonal-associated factor resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

Claim 35 part (a) requires that the promoter 'specifically' functions in supporting cells of the inner ear. The specification does not define the phrase "a promoter that specifically functions in supporting cells of the inner ear". The metes and bounds of the phrase are unclear.

The limitation "(b) a chimeric coat protein ablated for binding to a native adenovirus receptor and comprising a non-native ligand, which non-native ligand enhances uptake of the adenoviral vector by cells of the inner ear" recited in claim 35 part (b) is unclear in the following aspects: First, it is unclear if the phrase "comprising a non-native ligand, which non-native ligand enhances uptake of the adenoviral vector by cells of the inner ear" is modifying the recited chimeric coat protein, or the recited adenoviral vector, or the recited pharmaceutical composition, or something else. Second, the metes and bounds of the phrase "a chimeric coat protein ablated for binding to a native adenovirus receptor", as recited in claim 35, are unclear in the context of a *non-group C adenoviral vector.*

It is unclear whether chimeric viruses comprising both antigens of Group C in addition to antigens of another group (Groups A, for example) are considered to be non-group C adenoviral vectors. The specification, paragraphs [0024] and [0025] in particular, fails to define the term "non-group C adenoviral vectors" with respect to a chimeric viral coat. As an example, it is unclear whether an adenoviral vector comprising Ad5-Ad12 hexon capsid protein, i.e. a chimeric coat protein consisting of amino acid sequences of coat proteins originating from group C and group A adenovirus, See **Roy et al.,** Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998, is encompassed by the term "non-group C adenoviral vector" as recited in newly added claim 35 of instant application. Claims 36-53 depend from claim 35.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

3. Claims 35-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.* 37 CFR 1.118 (a) states that "No amendment shall introduce **new matter** into the disclosure of an application after the filing date of the application". *This new rejection is necessitated by claim amendments filed by Applicant on 11/13/2007.*

New independent claims 35 recites the limitation **(i)** "*a chimeric coat protein ablated for binding to a native adenovirus receptor*" in the context of *a non-Group C adenovirus vector* **(ii)** *"a promoter that specifically functions in supporting cells of the inner ear".* In the response filed on 11/13/2007, Applicant indicates that new claim 35 is supported by original claim 1, and by the specification at, e.g., paragraphs 0037, 0038, 0044, 0054, 0055, and 0071. The Examiner notes that original claim 1 does not recite these limitations, and the disclosure of paragraphs 0037, 0038, 0044, 0054, 0055, and 0071 of specification do not support the limitation either.

(i) The phrase "chimeric coat protein" is disclosed in the contexts pertaining to adenoviral coat proteins which mediate cell entry, e.g., the fiber and/or penton base, are absent or

disrupted (See paragraphs [0035] and [0036], US 2007/0141029, publication of instant application).

The phrase "ablated for binding to a native adenovirus receptor" is disclosed in the context pertaining to adenoviral capsid proteins (See paragraph [0038], US 2007/0141029, publication of instant application).

Taken together, it appears that the specification considers *fiber* and *penton base* protein as "coat proteins" as well as "capsid proteins". In other words, the specification use "coat proteins" and "capsid proteins" in an interchangeable manner, which is consistent with the teachings in the art that adenovirus capsids have three principle protein components: the hexon, the penton, and the fiber (See third paragraph, left column, page 1998, Introduction, Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998). . Moreover, the exemplary adenovirus receptor, coxsackie and adenovirus receptor (CAR), disclosed in the specification is the receptor for adenoviruses 2 and 5 (See **Bergelson et al.,** Isolation of a common receptor for Coxsackie B viruses and adenoviruses 2 and 5. *Science,* 275(5304):1320-3, 1997), and adenoviruses 2 and 5 belongs to subgroup C (See paragraph [0024], page 24, US 2007/0141028, publication of instant application). The specification does not disclose what is/are the native adenovirus receptor(s) of non-group C adenovirus, which is recited in claim 35. The exemplary adenovirus receptor, coxsackie and adenovirus receptor (CAR), disclosed in the specification is the receptor for adenoviruses 2 and 5 (See **Bergelson et al.,** Isolation of a common receptor for Coxsackie B viruses and adenoviruses 2 and 5. *Science,* 275(5304):1320-3, 1997), and adenoviruses 2 and 5 belongs to subgroup C

(See paragraph [0024], page 24, US 2007/0141028, publication of instant application). Accordingly, the specification does not provide written description regarding the information specific for the limitation "a chimeric coat protein ablated for binding to a native adenovirus receptor" in the context of a non-Group C adenovirus vector, as recited in claim 35. Furthermore, regarding whether at the time the application was filed, Applicant had possession of the claimed invention, it is noted that the post-filing arts of adenovirus indicate that the development of adenoviral vectors with new serotypes is an ongoing process. For instance, **Stone et al.** disclose the following: Originally, Ad vectors were based on the human Ad5 serotype and while most currently used Ad vectors are still based on Ad5, recent research has highlighted a series of problems that limit the efficacy and safety of these vectors. To circumvent the problems associated with Ad5-based vectors, new vectors have utilized various Ads of both human and nonhuman origin (See abstract, Stone et al., New serotypes of adenoviral vectors, *Curr Opin Mol Ther.* 8(5):423-31, 2006).

(ii) The specification discloses the following relevant to tissue specific promoter:

Preferably, the regulatory sequences comprise a tissue-specific promoter, i.e., a promoter that is preferentially activated in a given tissue and results in expression of a gene product in the tissue where activated. A tissue specific promoter for use in the inventive vector can be chosen by the ordinarily skilled artisan based upon the target tissue or cell-type. Suitable promoters include, but are not limited to, BRN.3C, BRN 3.1, the POU ORF3 factor promoter, BRK1, BRK3, the chordin promoter, the noggin promoter, the jagged1 promoter, the jagged2 promoter, and the notch1 promoter. Preferred tissue-specific promoters for use in the inventive method are specific to supporting cells or sensory hair cells, such as an atonal promoter or a myosin VIIa

promoter, which function in hair cells, or a hes-1 promoter, which functions in supporting cells. Ideally, a promoter is selected that promotes transgene expression in scarred epithelium (See paragraph [0055] of instant application.

It is noted that the specification does not define the term "specifically functions" in term of a promoter. Based on the commonly accepted scientific terminology, the term "a promoter that specifically functions ---" is interpreted as " the expression driven by the promoter is exclusive to ---" . In this regard, the specification does not disclose any of abovementioned promoters being specifically function in supporting cells of the inner ear. The relevant description is the statement "hes-1 promoter, which functions in supporting cells", however, there is no written description regarding the expression driven by hes-1 promoter being exclusive to the supporting cells of the inner ear, not any other cells or tissues.

Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), the MPEP 714.02, 3rd paragraph, last sentence and also the MPEP 2163.07, last sentence.

MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not

described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, and a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure.*

Enablement

4. Claims 35-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising an adenoviral vector comprising a nucleic acid sequence encoding an atonal-associated factor Math1 (also known as Hath1 and Atoh1) operably linked to a promoter that drives gene expression in supporting cells of the ear, wherein the nucleic acid sequence is expressed to produce Math1 in supporting cells of the inner ear resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear, **does not** reasonably provide enablement for an adenoviral vector that expresses *any* atonal-associated factor other than Math1 driven by a tissue specific promoter that drives expression specifically in the supporting cells of the inner ear. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. *This new rejection is necessitated by claim amendments filed by Applicant on 11/13/2007.*

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as

routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The basis of this scope of enablement is hinged on the lack of enabling support on the limitation "a promoter that specifically functions in supporting cells of the inner cell", as required in part (a) of claim 35.

The nature of the instant invention is drawn to a method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising an adenoviral vector comprising (a) a first nucleic acid sequence encoding an atonal-associated factor operably linked to a promoter that functions in supporting cells of the inner ear, wherein the first nucleic acid sequence is expressed to produce the atonal-associated factor resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

The breadth of the claims: claim 35 and its dependent claims 36-53 encompass a method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising an adenoviral vector, excluding Group C adenoviral vector, comprising a nucleic acid sequence encoding an atonal-associated factor operably linked to *any* promoter that functions in supporting cells of the inner ear, wherein the first nucleic acid sequence is expressed to produce the atonal-associated factor resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

With regard to promoter tissue specificity, the specification discloses that a tissue specific promoter for use in the inventive vector can be chosen by the ordinarily skilled artisan based upon the target tissue or cell-type. Suitable promoters include, but are not limited to, BRN.3C, BRN 3.1, the POU ORF3 factor promoter, BRK1, BRK3, the chordin promoter, the noggin promoter, the jagged1 promoter, the jagged2 promoter, and the notch promoter. However, it is noted that there is no disclosure in the specification that any of these promoter expresses exclusively in the supporting cells of inner ear, as recited in claim 35. The specification states that preferred tissue-specific promoters for use in the inventive method are specific to supporting cells or sensory hair cells, such as an atonal promoter or a myosin VIIa promoter, which function in hair cells, or a hes-1 promoter, which functions in supporting cells. Ideally, a promoter is selected that promotes transgene expression in scarred epitheliumn (See paragraph [0055], 2007/0141029, publication of instant application). In Example 2, the Math1 cDNA, which encodes an atonal-associated factor, is operatively linked to the cytomegalovirus immediate early (CMV) promoter. It is noted that a CMV promoter is a strong constitutive

promoter that does not express a linked coding sequence in a tissue specific manner. Rather, the CMV promoter is a constitutive promoter that functions ubiquitously in all tissues, which includes supporting cells of the inner ear. Claim 35 requires that the promoter 'specifically' functions in supporting cells of the inner ear. In this regard, the Examples 2-4 disclosed in the specification only indicates the Math 1 driven by CMV is expressed in the inner ear tissue, however, the Examples 2-4 do not demonstrate the Math1 driven by a CMV promoter being "specifically functions in support cells of inner ear", as recited in part (a) of claim 35. The specification fails to provide any guidance with respect to what promoters are active specifically in supporting cells of the inner ear as claimed.

In the art, the presence of tissue specific promoters that only express genes in a specific type of tissue has been well established. For instance, **Saukkonen et al.** teach various types of tissue specific promoters, including, for instance, hTERT (human telomerase reverse transcriptase) promoter being highly expressed only in tumor tissues, CEA (carcinoembryonic antigen) promoter being highly expressed in fetal tissue and being silent in adult tissue, and osteocalcin (OC) promoter being highly expressed only in bone tissues (See pages 686-687, section 4.2 Tissue-specific promoters, Saukkonen et al., Tissue-specific promoters for cancer gene therapy. *Expert Opin Biol Ther.* 4(5):683-96, 2004). Given the art-accepted definition of "specific" with regard to promoter activity and the lack of any other defining features of "specific" in the specification, it appears the specification has failed to provide even a single promoter that functions specifically in the supporting cells of the inner ear such that one of skill in the art could carry out the claimed invention.

With regard to therapeutic efficacy of changing the sensory perception of an animal upon delivery of an atonal-associated factor by an adenoviral vector, the specification only discloses direct injection of AdMath1.11D to the inner ear cells of guinea pigs (See Example 4, paragraph [0099], 2007/0141029, publication of instant application). Consistently, Staecker et al. (Applicant's own publication) reported direct injection of AdMath1.11D to the inner ear cells of guinea pigs (See abstract, and vector delivery, page 225, **Staecker et al.**, Vestibular hair cell regeneration and restoration of balance function induced by math1 gene transfer. *Otol Neurotol.* 28(2):223-31, 2007). It is noted that Math1 is also known as Atoh1 and Hath1 in the art (See abstract, **Kiernan et al.**, Sox2 is required for sensory organ development in the mammalian inner ear. *Nature*, 434(7036):1031-5, 2005). Neither the specification nor the art teaches changing the sensory perception of an animal upon delivery of an atonal-associated factor other than Math1 by an adenoviral vector. The specification has not provided any guidance as to what other atonal associated factor would have the same activity as Math1 such that use of such genes in place of Math1 would lead to the desired effect. Thus, the specification fails to enable use of any atonal associated factor other than Math1 in the claimed invention.

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention as recited in claims 35-53.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Previous rejection of claims 1, 3, 4, 16-20 under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103 (a) as obvious over Zheng et al. (Zheng et al., Overexpression of Math1 induces robust production of extra hair cells in postnatal rat inner ears. *Nat Neurosci.* 3(6): 580-6, 2000; listed as reference FF on the IDS filed by Applicant on 11/16/2006), is ***withdrawn*** because the claims 1-34 have been canceled and new claims 35-53 have been added.

Zheng et al. discloses expression of the Math-1 gene from a plasmid vector in rat cochlear explant tissues. However, Zheng et al. does not disclose (1) the use of an adenoviral vector, more specifically a non-group C adenoviral vector, as recited in newly added claim 35, comprising a nucleic acid sequence encoding an atonal-associated factor operably linked to a promoter that specifically functions in supporting cells of the inner ear, and (2) a non-group C adenoviral vector comprising a chimeric coat protein, as recited in part (b) of claim 35.

Neither did Zheng et al. suggests (1) the use of an adenoviral vector, more specifically a non-group C adenoviral vector, as recited in newly added claim 35, comprising a nucleic acid sequence encoding an atonal-associated factor operably linked to a promoter that specifically functions in supporting cells of the inner ear, and (2) a non-group C adenoviral vector comprising a chimeric coat protein, as recited in part (b) of claim 35.

6. Previous rejection of claims 1-6, 8-10 and 16-21 under 35 U.S.C. 102(e) as being anticipated by Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), is ***withdrawn*** because the claims 1-34 have been canceled and new claims 35-53 have been added.

Zoghbi et al. also disclose such a method wherein the animal is a human, the atonal associated factor is MATH1, HATH1, the vector is a viral vector, an adenoviral vector, an adeno-associated viral vector, replication deficient (E1) adenoviral vector, and the hair cells are generated from adult differentiated cells of inner ear (see col.139, claims 1-8, and col. 47, lines 37-56, col. 48, example 16). However, Zoghbi et al. does not disclose (1) the use of an adenoviral vector, more specifically a non-group C adenoviral vector, as recited in newly added claim 35, comprising a nucleic acid sequence encoding an atonal-associated factor operably linked to a promoter that specifically functions in supporting cells of the inner ear, and (2) a non-group C adenoviral vector comprising a chimeric coat protein, as recited in part (b) of claim 35.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The rejection of claims 1, 6, 8-12 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Kovesdi et al (US patent 6,821,775, issue date, Nov. 23, 2004), is ***withdrawn*** because the claims 1-34 have been canceled and new claims 35-53 have been added.

Neither Zoghbi et al., 2005 nor Kovesdi et al., 2004 disclose (1) a non-group C adenoviral vector, and (2) a non-group C adenoviral vector comprising a chimeric coat protein, as recited in part (b) of claim 35.

8. The rejection of claims 1, 13-15 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Staecker et al. (Staecker et al., Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell loss. *Otolaryngol Head Neck Surg.* 119(1): 7-13, 1998; listed as reference EU on the IDS filed by Applicant on 11/16/2006), is ***withdrawn*** because the claims 1-34 have been canceled and new claims 35-53 have been added.

Neither Zoghbi et al., 2005 nor Staecker et al., 1998 disclose (1) a non-group C adenoviral vector, and (2) a non-group C adenoviral vector comprising a chimeric coat protein, as recited in part (b) of claim 35.

9. The rejection of claims 35-40, 43, 49-51, and 53 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Roy et al., (Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998)

Claim interpretation: It is noted that the specification fails to define the term "non-group C adenoviral vectors" with respect to a chimeric viral coat ablated for binding to a native adenovirus receptor. The broadest reasonable interpretation of the limitation "a chimeric viral coat ablated for binding to a native adenovirus receptor under" reads on a chimeric Ad5-Ad12 hexon protein, i.e. a chimeric Group C-Group A coat protein, even though there is a portion of Ad5 hexon sequences and the entry of adenoviral vector with chimeric Ad5-Ad12 hexon protein is mediated by unidentified receptor.

Zoghbi et al. disclose a method of generating hair cells for an animal comprising delivering directly to an inner ear of said animal an atonal associated nucleic acid encoding a polypeptide having at least about 80% identity to MATH1 (SEQ ID NO: 58) (see lines 15-22, col. 1 and col. 139, claims 1-8), and MATH1 is a transcription factor belonging to the basic helix-loop-helix (bHLH) family of proteins (See lines 30-32, col. 1). Zoghbi et al. also disclose such a method wherein the animal is a human, the atonal associated factor is MATH1, HATH1, the vector is a viral vector, an adenoviral vector, an adeno-associated viral vector, replication deficient (E1) adenoviral vector, and the hair cells are generated from adult differentiated cells of inner ear (see col.139, claims 1-8, and col. 47, lines 37-56, col. 48, example 16). Zoghbi et al. further disclose that different methods of delivery can be utilized to administer a vector into a

cell. Examples include: (1) methods utilizing physical means, such as electroporation (electricity), a gene gun (physical force) or applying large volumes of a liquid (pressure); and (2) methods wherein said vector is complexed to another entity, such as a liposome, viral vector or transporter molecule (which binds to cell surface receptor, see col. 27, 2nd paragraph) (reading on claim 21 of instant application).

With regard to therapeutic effect by expressing Math1 in treating hearing loss and balance disorder (claims 36-38 of instant application), Zoghbi et al. teach methods of treating an animal, including a human, for cerebellar granule neuron deficiencies, for generating hair cells, for treating hearing impairment or an imbalance disorder by administration of a vector expressing the atonal associated factor (MATH1 or HATH1) (See for instance, second paragraph, col. 5).

With regard to hes-1 promoter (claim 39 of instant application), Zoghbi et al. teaches that it is also possible, and often desirable, to use promoter or control sequences normally associated with the Math1 gene sequence, provided such control sequences are compatible with the host cell systems or the target cell (See Example 15). In this regard, Zoghbi et al. cites Zine et al., 2001, which taught that Hes1 and Math1 are expressed in the developing cochlea of inner ears (Zine et al., Hes1 and Hes5 activities are required for the normal development of the hair cells in the mammalian inner ear, *The Journal of Neuroscience*, vol. 21, pp. 4712-4720, 2001).

However, Zoghbi et al. do not teach an adenoviral vector comprising a chimeric coat protein.

Regarding an adenoviral vector comprising a chimeric coat protein, Roy et al. teaches adenovirus capsids (i.e. coat proteins) have three principal protein components: the hexon, the

penton, and the fiber, and there are at least 49 different serotypes of adenovirus have been described, including serotypes 35 and 41, that are classified into six different subgroups, A, B, C, D, E and F (See third paragraph, introduction, page 6875, and cited reference by Horwitz, 1990). Roy et al. further teaches an adenovirus vector with a chimeric Ad5-Ad12 hexon, which is a component of fiber trimer coat protein structure (See abstract and Figure 1, Roy et al., 1998). The chimeric Ad5-Ad12 hexon is considered as a non-native ligand, which enhances uptake of the adenoviral vector upon administered to the inner ear by circumvention of host immunity to the adenovirus coat protein.

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor to the inner ear of a subject as taught by Zoghbi et al. using the adenoviral vector with Ad5-Ad12 chimeric coat protein that circumvents host immunity taught by Roy et al. because the presence of antibodies to the capsid proteins prevent efficacious adenovirus vector administration *in vivo*. As such, the ordinary artisan would have been motivated to use the vector of Roy *et al* to deliver atonal associated nucleic acid *in vivo* because its effectiveness in expressing the gene of interest *in vivo* without provoking undesired host immunity to the adenoviral vector. The level of skill in art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with a chimeric coat protein, and deliver it to inner ear to generate sensory hair cells. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

10. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Roy et al. (Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998) as applied to claims 35 and 40 above, and further in view of Kovesdi et al. (US patent 6,821,775, issue date, Nov. 23, 2004).

Claim interpretation: It is noted that the specification fails to define the term "non-group C adenoviral vectors" with respect to a chimeric viral coat ablated fro binding to a native adenovirus receptor. The broadest reasonable interpretation of the limitation "a chimeric viral coat ablated fro binding to a native adenovirus receptor under" reads on a chimeric Ad5-Ad12 hexon protein, i.e. a chimeric Group C-Group A coat protein, even though there is a portion of Ad5 hexon sequences and the entry of adenoviral vector with chimeric Ad5-Ad12 hexon protein is mediated by unidentified receptor.

The teachings of Zoghbi et al. and Roy et al. are set forth in the rejection of claims 35-40, 43, 49-51, and 53 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Roy et al., (Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998).

However, neither Zoghbi et al. nor Roy et al. teach such a method wherein an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region.

Regarding an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region, Kovesdi et al. teach a replication deficient adenoviral vector with deletion of E1 and E4 and further comprise a pGUS spacer in the E4 region (see second paragraph, col. 7

and claim 1). Kovesdi et al. also disclose that said vector is used to deliver therapeutic effective amount of PEDF to eyes of mice to promote neovascularization. Kovesdi et al. further discloses that in the absence of a spacer, production of fiber protein and/or viral growth of the multiply replication deficient adenoviral vector is reduced by comparison to that of a singly replication deficient adenoviral vector. However, inclusion of the spacer in at least one of the deficient adenoviral regions, preferably the E4 region, counteracts this defect in growth and fiber expression (See third paragraph, col. 6, and claim 1). It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor to the inner ear of a subject as taught by Zoghbi et al. using the adenoviral vector with Ad5-Ad12 chimeric coat protein that circumvents host immunity taught by Roy et al. because the presence of antibodies to the native capsid proteins prevent efficacious adenovirus vector administration *in vivo*. It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by combined teachings of Roy et al. and Kovesdi et al. in the method of generating hair cells to deliver atonal associated nucleic acid to inner ear of a subject taught by Zoghbi et al. since the vector taught by combined teachings of Roy et al. and Kovesdi et al. that circumvents host immunity due to the presence of a chimeric coat protein, and that is able to counteract the defect in growth of the E1/E4 deficient ADV and the defect in expression of the chimeric coat. As such, the ordinary artisan would have been motivated to use this vector to deliver atonal associated nucleic acid *in vivo* because its effectiveness in expressing a gene of interest *in vivo* without provoking undesired host immunity to the adenoviral vector and capable of expressing the engineered chimeric coat protein a Kovesdi et al. discloses that in the absence of a spacer, production of fiber protein and/or viral

growth of the multiply replication deficient adenoviral vector is reduced by comparison to that of a singly replication deficient adenoviral vector; however, inclusion of the spacer in at least one of the deficient adenoviral regions, preferably the E4 region, counteracts this defect in growth and fiber expression (See third paragraph, col. 6, and claim 1).

One of ordinary skill in the art would have reasonable expectation of success in delivering an atonal associated nucleic acid sequence such as Math1, to inner ear to generate sensory hair cells because the adenoviral vector comprises engineered chimeric coat protein taught by Roy et al., can be properly expressed in the E1/E4 deficient adenoviral vector taught by Kovesdi et al. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

11. Claims 45-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Roy et al. (Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998) as applied to claim 35 above, and further in view of Staecker et al. (Staecker et al., Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell loss. *Otolaryngol Head Neck Surg.* 119(1): 7-13, 1998; listed as reference EU on the IDS filed by Applicant on 11/16/2006).

Claim interpretation: It is noted that the specification fails to define the term "non-group C adenoviral vectors" with respect to a chimeric viral coat ablated fro binding to a native adenovirus receptor. The broadest reasonable interpretation of the limitation "a chimeric viral

coat ablated fro binding to a native adenovirus receptor under" reads on a chimeric Ad5-Ad12 hexon protein, i.e. a chimeric Group C-Group A coat protein, even though there is a portion of Ad5 hexon sequences and the entry of adenoviral vector with chimeric Ad5-Ad12 hexon protein is mediated by unidentified receptor.

The teachings of Zoghbi et al. and Roy et a. are set forth in the rejection of claims 35-40, 43, 49-51, and 53 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Roy et al., (Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998).

However, neither Zoghbi et al. nor Roy et al. teach such a method wherein a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor.

Regarding a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor, Staecker et al. teach brain-derived neurotrophic factor (BDNF) gene therapy prevents spiral ganglion degeneration after hair cell loss by supporting the survival of auditory neurons (see abstract, bridging paragraph between left and right columns, page 10, and Figure 5).

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor to the inner ear of a subject as taught by Zoghbi et al. using the adenoviral vector with Ad5-Ad12 chimeric coat protein that circumvents host immunity taught by Roy et al. because the presence of

antibodies to the native capsid proteins prevent efficacious adenovirus vector administration *in vivo*. It would have been obvious to one of ordinary skill in the art to co-administer neurotrophic agent such as BDNF with atonal associated factor in the method of changing sensory perception based on the combined teaching of Zoghbi et al., Roy et al., and Staecker et al. One of ordinary skill in the art would have been motivated to include BDNF in the claimed method because it has been shown by Staecker et al. to support the survival of auditory neurons. If the ordinary artisan intends to generate hair cells and improve hearing after hearing loss, the ordinary artisan would be motivated to preserve the auditory neurons which are vital for hearing. The level of skill in the art is high. One of ordinary skill in the art would have reasonable expectation of success to co-administer the BDNF with atonal associated factor using a separate or the same vector in the method taught by Zoghbi et al. and Roy et al because of the demonstration that the presence of a chimeric coat protein can circumvent host immunity by combined teachings of Zoghbi et al. and Roy et al., and the demonstration that brain-derived neurotrophic factor (BDNF) gene therapy prevents spiral ganglion degeneration after hair cell loss by supporting the survival of auditory neurons by the teachings of Staecker et al. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

12. Claims 44 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Roy et al. (Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998) as applied to claims 35 and 43 above, and further in view of Kovesdi et al. (US patent 6,821,775, issue date,

Nov. 23, 2004) and Wickham et al. (Wickham et al., US 6,455,314, issued 09/24/2002; This patent is listed as reference BM on the IDS filed by Applicant on 11/16/2006).

Claim interpretation: It is noted that the specification fails to define the term "non-group C adenoviral vectors" with respect to a chimeric viral coat ablated fro binding to a native adenovirus receptor. The broadest reasonable interpretation of the limitation "a chimeric viral coat ablated fro binding to a native adenovirus receptor under" reads on a chimeric Ad5-Ad12 hexon protein, i.e. a chimeric Group C-Group A coat protein, even though there is a portion of Ad5 hexon sequences and the entry of adenoviral vector with chimeric Ad5-Ad12 hexon protein is mediated by unidentified receptor.

The teachings of Zoghbi et al., Roy et al., and Kovesdi et al. are set forth in the rejection of claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Roy et al. (Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998) as applied to claims 35 and 40 above, and further in view of Kovesdi et al. (US patent 6,821,775, issue date, Nov. 23, 2004).

However, Zoghbi et al. and Roy et al. and Kovesdi et al. do not teach such a method with an alternatively targeted adenovirus.

Regarding an adenoviral vector with altered target cells, Wickham et al, teaches that coxsackievirus and adenovirus receptor (CAR) is the receptor for adenovirus serotype 2 and 5, citing (Bergelson et al., Science, 275, 1320-23 (1997) (See lines 35-40, col. 1), and mutations

reducing affinity of adenovirus for the CAR protein (See Table 2 and Table 3). Wickham et al, also teaches an adenovirus can include any suitable ligand for altering tropism of the virus, and non-native ligand of adenovirus can be synthetic peptide sequences such as polyamino acids (e.g., polylysine and/or arginine) (See lines 33-39, col. 11, for instance).

It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by combined teachings of Roy et al. and Kovesdi et al. in the method of generating hair cells to deliver atonal associated nucleic acid to inner ear of a subject taught by Zoghbi et al. since the vector taught by combined teachings of Roy et al. and Kovesdi et al. that circumvents host immunity due to the presence of a chimeric coat protein, and that is able to counteract the defect in growth of the E1/E4 deficient ADV and the defect in expression of the chimeric coat. It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by combined teachings of Roy et al., Kovesdi et al. and Wickham et al. in the method of generating hair cells to deliver atonal associated nucleic acid to inner ear of a subject taught by Zoghbi et al. since the vector taught by combined teachings of Roy et al. and Wickham et al. that circumvents host imminity and successfully targets adenovirus to different cell types *in vivo,* as such, the ordinary artisan would have been motivated to use this vector to deliver atonal associated nucleic acid *in vivo* because its effectiveness in expressing the gene of interest *in vivo* in desired target cell types, without provoking undesired host immunity to the adenoviral vector. The level of skill in art of molecular cloning is high.

One of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with altered coat protein, and deliver the adenoviral vector to desired target cells in inner ear to generate sensory hair cells because the adenoviral vector comprises

engineered chimeric coat protein taught by Roy et al., can be properly expressed in the E1/E4 deficient adenoviral vector taught by Kovesdi et al., and the altered ligand-receptor interaction taught by Wickham et al. can result in the adenoviral virus targeting to desired cells. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

13. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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